67 Legare Street, #403
Charleston, SC 29401
November 23, 1998

Dr. Larry Hart
Executive Secretary
National Toxicology Program
Board of Scientific Counselors
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Hart:

More than a decade ago, I served as a principal investigator of a CDC-sponsored multi-center study of cancer in relation to potential military exposure to Agent Orange. Since that time, I have remained involved with epidemiologic research on human health in relation to exposure to dioxin-like compounds. That involvement included service as an invited observer of the 1997 IARC working group evaluation of the carcinogenicity of dioxin. Last year, I prepared written comments for the NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee and made a brief oral presentation at the Subcommittee meeting.

The Chlorine Chemistry Council has asked me to provide the Subcommittee with an updated independent scientific evaluation of this topic. The attached comments are submitted to the Subcommittee in order to help clarify issues related to the 1997 IARC working group evaluation and the epidemiologic literature that has been published subsequently. This critique is based upon my own personal judgment as a cancer epidemiologist, provost of an academic health science center, and former public health dean.

I hope that the Subcommittee will find these comments to be helpful. I plan to attend the upcoming meeting of the Subcommittee and would be grateful for the opportunity to make a few remarks to the Subcommittee at that time. Thanks in advance for your consideration.

Sincerely,

Raymond S. Greenberg, MD, PhD

Enclosure

Comments on: RC Draft Background Document for TCDD and Supplement

Raymond S. Greenberg, MD, PhD
Charleston, SC

Executive Summary

In 1997, the International Agency for Research on Cancer (IARC) reviewed the scientific evidence on the potential carcinogenicity of dioxins. That review concluded that: "There is *limited evidence* in humans for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD)" (p. 342). The IARC Working Group found that the epidemiologic evidence was not sufficient to establish causality for several reasons. First, strength of exposure-disease relationships is one of the principal criteria for judging causality in epidemiologic studies. The statistical associations between exposure to TCDD and risk of cancer are very weak. Second, the cancer outcome most consistently linked to TCDD exposure in these studies is the aggregation of all cancers combined. There is little precedent in epidemiology for a causal risk factor to be associated with all types of cancer combined, without stronger associations to particular types of cancer. Third, confounding by other exposures could not be excluded from some of the observed associations. Although additional epidemiologic studies of this topic have appeared in the peer-reviewed literature since the time of the IARC review, the key data from virtually all of these reports were published in preliminary form prior to the IARC review and were cited in the IARC document. The small amount of truly new epidemiologic information that has appeared since the IARC review does not support any change in the classification of this compound with respect to carcinogenicity.

A. Comments on the Draft Background Document:

1. The Draft Background Document misrepresents one of the most important conclusions of the IARC Working Group. On p. RC-1, lines 17-18, the Background Document states that: "In the highly exposed industrial sub-cohorts, a *causal* (my emphasis) relationship between TCDD exposure and mortality from all cancers combined was noted . . ." The Background Document later reiterates this claim on p. 3-2, lines 6-8: "In its summary of the epidemiological evidence for the most highly exposed populations, the IARC Working Group identified a *causal* (again, my emphasis) association between TCDD exposure and all cancer combined . . ." In actuality, the IARC report clearly stated that the "lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiological findings must be treated with caution" (p. 337). Most importantly, the IARC Working Group concluded that "there is *limited evidence* in humans for the carcinogenicity" of TCDD (p. 342).

2. The Draft Background Document overstates the extent to which literature published since the IARC Working Group report provides new information. For instance on p. RC-1, lines 19-23, the Background Document indicates that: "Increased risk for certain cancers was also reported in a *new* (my emphasis) study of the Seveso, Italy, dioxin-exposed population (Bertazzi et al., 1998 [in press]). These additional findings were not considered in the IARC evaluation and further strengthen the association between dioxin-exposure and human cancer." The paper in question was not a *new* study. Rather, it was an update of a cohort that has been followed since 1976. Findings from this study have appeared multiple times in the peer-reviewed literature as cited in the report of the IARC Working Group (Bertazzi et al., *Am. J. Epidemiol.*, 1989;**129**:1187-99 and Bertazzi et al., *Organohalogen Compounds* 1996;**30**:294-6). The so-called 'new' findings were presented in Table 33 of the IARC report (pp. 146-7) and in the corresponding text (p. 161). The only aspect of the 'new' findings that was not included in the IARC report was a subanalysis by latency. The IARC Working Group was aware of these results, but did not include them in the report because they had not been accepted yet for publication in the peer-reviewed literature.

3. The Draft Background Document does not provide a balanced discussion of whether dose of exposure to TCDD appears to be related to risk of cancer occurrence in humans. On p. 3-2, Lines 2-3, the Document indicates that: "In the largest and most heavily exposed German cohort, a dose-response relationship was noted for overall cancer mortality." The Draft Background Document fails to note that dioxin measurements were made on only 15% of this cohort and that the sampled individuals were certainly not a random subset of the entire cohort. Equally important, the Draft Background Document does not mention that the response was flat across all levels of dose except for a single outlying elevation in the highest exposure category. The authors inappropriately assessed the statistical significance of the relationship with a test for linear trend, despite the fact that the underlying risk pattern clearly was not linear. Finally, the citation for this dose-response relationship is a published erratum (Flesch-Janys et al., *Am. J. Epidemiol.*, 1996;**144**:716). In their original calculations, the authors used an incorrect follow-up date, which led to an overestimation of relative risks and overstatement of the statistical significance of individual point estimates. The history of computational inaccuracies in such important data does not instill confidence in these findings.

B. Comments on the Supplement:

Section 2 of the Supplement briefly describes various updates of epidemiologic studies published during 1997 and 1998 and Section 3 provides a bibliography of these references. Of the ten references cited, five appeared in a supplement to *Environmental Health Perspectives*, and are the written versions of invited talks at a November 1996 meeting at the German Cancer Research Center. This meeting in

Heidelberg preceded the IARC Working Group meeting by four months. One of the IARC epidemiology panel members (Dr. Becher) co-hosted the Heidelberg meeting and several of the other epidemiology panel members attended the Heidelberg meeting, including three who presented papers there (Drs. Becher, Bertazzi and Kogevinas). The results presented in these five supplementary papers, therefore, were well known to the members of the IARC Working Group.

1. Previously Highlighted Supplementary Reports

Of the ten cited supplementary references, two were given special attention in either the Draft Background Document or the meeting of the Report on Carcinogens Subcommittee in October 1997.

a) Bertazzi et al., *Epidemiol.*, 1997;8:646-52.

The Draft Background Document makes repeated reference to the update of the Seveso cohort, which at that time was in press and subsequently, published (Bertazzi et al., *Epidemiol.*, 1997;**8**:646-52). Last year, I provided comments on this paper for the benefit of the Subcommittee. The essence of this critique is summarized below, with a complete copy of my earlier comments reproduced as an appendix to this current submission.

i) A large number of separate analyses were conducted by Bertazzi et al., stratified by exposure zone, gender, and cancer type. Of the 159 outcomes, eight reached statistical significance at the 0.05 level; this is exactly the number of positive associations that one would have expected by chance alone.

ii) The results reported by Bertazzi et al. lacked internal consistency. For example, in zone B apparent excesses of respiratory cancer and leukemia were observed among males, with apparent deficits for these same sites among females.

iii) The pattern of positive results reported by Bertazzi et al. is random, with no apparent dose-response gradient. In the highest exposure zone for example, males actually experienced less than half of the cancers that were expected. For digestive cancer, a grouping highlighted by the authors as potentially associated with exposure, males in the highest exposure zone experienced a borderline statistically significant 80% deficit.

iv) The findings reported by Bertazzi et al. are largely inconsistent with other studies of human populations heavily exposed to dioxin. Aggregating results across exposure zones and genders, no excesses were observed for all cancers combined (Relative Risk

= 0.93), lung cancer (Relative Risk = 0.95), non-Hodgkin's lymphoma (Relative Risk = 0.92), or soft tissue sarcoma (Relative Risk = 1.0).

v) By combining all digestive disease cancers into a single site, Bertazzi et al. used an unconventional classification. This aggregation includes sites as diverse as the pancreas, liver, stomach, colon, and rectum. These sites are not only distinct anatomically, histologically and physiologically; they also have markedly different epidemiologic risk factor profiles. Therefore, it makes little sense from an epidemiologic perspective to treat them as a single category.

vi) Latency analyses were presented by Bertazzi et al. only for selected anatomic sites and for only one exposure zone. No tests of statistical significance were performed. As in other analyses, a lack of consistency across genders also was observed for latency.

vii) The possibility of confounding was not thoroughly explored by Bertazzi et al. For example, three pleural cancers were observed for males in zone B (a fivefold increase), but no attempt was made to assess the possible role of asbestos exposure.

b. Hooiveld et al., *Am. J. Epidemiol.*, 1998;147:891-901. At the October 1997 Report on Carcinogens Subcommittee meeting, Dr. Arnold Schecter was invited to present to the Subcommittee the rationale for listing TCDD as a known human carcinogen. In his presentation, Dr. Schecter included data from a report by Hooiveld et al. that was not published in the peer-reviewed literature at the time and was not included in the Draft Background Document. In the interim, the paper by Hooiveld et al. was published (*Am. J. Epidemiol.*, 1998;147:891-901). In June 1998, I provided the Subcommittee with some written comments on the paper by Hooiveld et al. The essence of my critique is summarized below, with a complete copy of my earlier comments reproduced as an appendix to this current submission.

i) Although Dr. Schecter implied that the results reported by Hooiveld et al. were new additions to the literature, the main findings of this paper were published previously (*Organohalogen Compounds* 1996;30:185-9) and this population was one of four industrial cohorts given particular emphasis in the IARC monograph (Table 38).

ii) The findings presented by Hooiveld et al. revealed a generalized increase in mortality, without any clear specificity with particular outcomes. This lack of specific exposure-disease relationships violates one of the basic tenets of causal reasoning in epidemiology and raises the possibility of a systematic error in the comparison of observed with expected mortality.

iii) The findings reported by Hooiveld et al. reveal inconsistencies with those reported in other cohorts. For example, the Dutch cohort suggests high elevations in risk of bladder and renal cancer that are not seen in other dioxin-exposed industrial cohorts.

This type of inconsistency suggests the possibility that the Dutch workers were exposed to other carcinogens.

iv) The results presented by Hooiveld et al. concerning back-calculated TCDD levels must be viewed with particular caution. Only 4% of the cohort had serum measurements obtained, and two-thirds of those selected for blood sampling did not have useable results.

v) The dose-response relationships presented by Hooiveld et al. do not demonstrate a clear gradient of effect. For example, the risk of urinary cancers rose from low to medium exposure, only to fall back to baseline in the highest exposure group. For all cancers combined and for lung and respiratory cancer, no increase in risk was observed between the medium and highest exposure groups.

2. Other Supplementary Reports:

a) **Becher and Flesch-Janys, *Environ. Health Perspect.*, 1998;106(Suppl. 2):623-4.** This is an overview of the November 1996 symposium hosted by the German Cancer Research Center. It is a summary of the meeting and provides no additional data.

b) **Becher et al., *Environ. Health Perspect.*, 1998;106(Suppl. 2):663-70.** This publication derives from the November 1996 symposium hosted by the German Cancer Research Center. It provides a reanalysis of the dose-response relationship that was published previously (*Am. J. Epidemiol.*, 1995;**142**:1165-76 and erratum *Am. J. Epidemiol.*, 1996;**144**:716). The earlier results were cited in the report of the IARC Working Group. Additional comments on this paper follow:

i) Where categorical results were presented in the recent publication, the categories used for analysis were quite different from those presented in the earlier work. The authors do not explain the reasons for changing the categorization scheme.

ii) The updated dose-response relationship did not reach the level of statistical significance previously reported by the authors and cited within the report of the IARC Working Group.

iii) Although Becher et al. indicated that analyses were conducted for both all cancer combined and lung cancer, only the results for all cancer combined were presented. It is unclear why the authors did not present the lung cancer results.

c) **Bertazzi et al., *Environ. Health Perspect.*, 1998;106(Suppl. 2):625-33.** This publication is the written version of the paper orally presented at the November 1996 meeting at the German Cancer Research Center. The cancer outcome data are

identical to those presented by Bertazzi et al. in the publication (*Epidemiol.*, 1997;8:646-52) cited in the Draft Background Document. The same reservations cited above, therefore, apply to this publication as well.

d) Flesch-Janys et al., *Environ. Health Perspect.*, 1998;106(Suppl. 2):655-62. The cohort presented in this analysis is the same one presented in the paper by Flesch-Janys et al. (*Am. J. Epidemiol.*, 1995;**142**:1165-76) that was cited in the report of the IARC Working Group.

i) The model developed by the authors could explain only about one-quarter of the variability that was observed in serum levels of TCDD.

ii) The observed mortality from all causes in this cohort was higher than expected based upon mortality in the general population. This is a highly unusual finding for any working population, as workers tend to be healthier than the population at large (the healthy worker effect). This finding is in direct conflict with most other industrial cohorts of TCDD-exposed workers. It is unlikely that such an apparent generalized increase in mortality occurred because of a causal association with TCDD exposure and more likely represents some systematic error in effect estimation.

iii) No gradient of risk of lung cancer was observed using either TCDD or TEQ dose levels, arguing against a causal association.

iv) No gradient of risk of hematopoietic and lymphatic cancer was observed using either TCDD or TEQ dose levels, arguing against a causal association.

v) The risk gradient for all cancers combined with TEQ (that was cited in the report of the IARC Working Group as evidence of a dose-response relationship) was not observed in this analysis. As previously noted, dose-response analyses published by these authors on the same data set were the subject of a published erratum. In light of previous calculation errors and continuing apparent discrepancies in reported results, it is difficult to assign much weight to this evidence.

e) Hay et al., Ann. N. Y. Acad. Sci., 1997;837:138-59.

i) This is a study of phenoxy herbicide applicators. Although mentioned in the report of the IARC Working Group, studies of these types of populations were not given much weight. To quote the report directly: "In these studies, direct evidence of exposure to 2,3,7,8-TCDD is often lacking. The limited data available indicate that exposure to 2,3,7,8-TCDD is likely to be substantially lower than exposure in industrial cohorts" (p. 165). The present study did not have access to direct measurements of TCDD exposure, and there is no reason to believe that exposure was higher than other applicator populations.

ii) The study population was small (N =225), and thus estimates of outcomes were imprecise, as reflected by very broad confidence intervals.

iii) Overall mortality in this population of workers was 50% higher than would be expected based upon mortality in the general population. As stated for the preceding paper, the absence of a healthy worker effect across all causes of death is unlikely to arise from a causal association with a work-related exposure. More likely, this pattern suggests a systematic error in effect estimation.

iv) These workers were exposed to a variety of chemicals, including 2,4-D and 2,4,5-T, as well as polychlorinated biphenyls and polychlorinated dibenzofurans. It is impossible, therefore, to assign to 2,3,7,8-TCDD as the cause of any observed increase in overall or cancer mortality.

f) Kogevinas et al., *Am. J. Epidemiol.*, 1997;145:1061-75.

i) This paper was included in the report of the IARC Working Group as it had been accepted for publication and was in press at the time of the meeting. Data from this report were cited in Table 38 of the IARC report and thus were highlighted in the conclusions that were drawn at that time.

ii) The observed small excess of mortality from all cancers combined in this cohort did not correlate with duration of exposure, a proxy of dose. The absence of a gradient of risk with increasing dose argues against a causal interpretation. The authors were appropriately circumspect in their interpretation of this finding, stating that: "exposure to . . . TCDD and other chlorinated dioxins *may* (my emphasis) be associated with a small increase in overall cancer risk."

iii) The observed small excess of lung cancer mortality in this cohort also did not correlate with duration of exposure, and thus is unlikely to represent a causal association.

iv) The observed small excess of non-Hodgkin's lymphoma mortality in this cohort did not correlate with duration of exposure, and thus is unlikely to represent a causal association.

v) The observed modest excess of soft tissue sarcoma mortality is entirely attributable to the U.S. cohorts included in the NIOSH investigation (Fingerhut et al., *N. Engl. J. Med.*, 1991;324:212-18). Lack of confirmation in any of the other international cohorts and the absence of a monotonic dose-response relationship argues against a causal interpretation.

g) Lynge, *Environ. Health Perspect.*, 1998;106(Suppl. 2):683-8.

i) This cohort was included in the report of the IARC Working Group.

ii) No excess risk was observed for all types of cancers combined.

iii) No excess risk was observed for lung cancer.

iv) Small excesses in risk of soft tissue sarcoma and non-Hodgkin's lymphoma were observed, but these results were not statistically significant. The soft-tissue sarcomas occurred in workers with relatively short duration of exposure (two subjects were only three months in the plant), and thus, it is unlikely that these outcomes reflect an underlying causal relationship with exposure to TCDD.

h) Michalek et al., *Am. J. Epidemiol.*, 1998;148:786-92.

i) This report provides the mortality experience through 1993 of veterans of Operation Ranch Hand, the military unit responsible for aerial spraying of herbicides in Vietnam. These findings were reported previously (Ketchum and Akhtar, Interim Technical Report AL/AO-TR-1996-0068, 1996) and were included in the report of the IARC Working Group.

ii) There were fewer cancer deaths among exposed veterans than were expected.

iii) The subgroup of veterans with the highest measured serum dioxin levels (enlisted ground personnel) did not demonstrate any increased risk of cancer.

iv) A small excess of lung cancer deaths was observed among veterans followed at least 20 years, but chance could not be excluded as an explanation for this finding.

v) The sample size was too small to evaluate the risks of other specific types of cancer.